DETAILED ACTION

Status of the Application

[1] Claims 22-24, 30-32, and 35-36 are pending in the application.

[2] Applicant's amendment to the claims, filed on 6/10/11, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's remarks filed on 6/10/11 in response to the non-final Office action mailed on 2/10/11 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections previously applied to claims 37-41 are withdrawn solely in view of the amendment to cancel these claims.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[5] The objection to claims 22, 24, and 30 in the recitation of "protein(Y) is a nucleic acid sequence encoding mini-proinsulin; R in As_mR is an..." is withdrawn in view of the instant amendment to claims 22, 24, and 30.

Claim Rejections – Double Patenting

[6] The rejection of claims 31 and 35 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of US Patent

7,638,618 B2 (hereafter "'618 patent") is maintained for the reasons of record and the reasons set forth below.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). In view of the recitation of the transitional phrase "comprising" in claim 31, each of the individual moieties of the nucleic acid of claim 31, *i.e.,* Px, Sx, etc., can include additional unrecited elements. The difference between claim 1 of the '618 patent and claims 31 and 35 herein is that claims 31 and 35 require Px to be a yeast ADH2 promoter and Sx to be an alpha factor leader sequence, otherwise, claim 1 of the '618 patent anticipates claims 31 and 35 of this application when Z_1 or Z_2 of claim 1 the '618 patent is a codon for arginine.

Claims 31 and 35 cannot be considered patentably distinct over claim 1 of the '618 patent when there is a specifically disclosed embodiment in the '618 patent that supports claim 1 of the patent and falls within the scope of claims 31 and 35 herein because it would have been obvious to one of ordinary skill in the art to include a yeast ADH2 promoter sequence as Px and an alpha factor leader sequence as Sx in claim 1 of the '618 patent by selecting a specifically disclosed embodiment that supports that claim. See, *e.g.,* column 6, lines 32-35 of Example 1 of the '618 patent, which

specifically exemplifies a nucleic acid encoding a hirudin-miniproinsulin fusion protein with a yeast ADH2 promoter sequence and an alpha factor leader sequence. One of ordinary skill in the art would have been motivated to include a yeast ADH2 promoter sequence and an alpha factor leader sequence because that embodiment is specifically disclosed as a working example within claim 1 of the '618 patent.

[7] The rejection of claims 22-24, 30, and 36 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-6 of the '618 patent in view of Dörschug et al. (US Patent 6,875,589; cited in the PTO-892 mailed on 12/12/08; hereafter "Dörschug") is maintained for the reasons of record and the reasons set forth below.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 22-24, 30, and 36 cannot be considered patentably distinct over claims 5-6 of the '618 patent when there is a specifically disclosed embodiment in the '618 patent that supports claims 5-6 of the '618 patent and falls within the scope of

claim 41 herein because it would have been obvious to one of ordinary skill in the art to include a yeast ADH2 promoter sequence as Px and an alpha factor leader sequence as Sx in the nucleic acid of the yeast host cells claims 5-6 of the '618 patent by selecting a specifically disclosed embodiment that supports that claim. See, *e.g.*, column 6, lines 32-35 of Example 1 of the '618 patent, which specifically exemplifies a nucleic acid encoding a hirudin-miniproinsulin fusion protein with a yeast ADH2 promoter sequence and an alpha factor leader sequence. One of ordinary skill in the art would have been motivated to include a yeast ADH2 promoter sequence and an alpha factor leader sequence because that embodiment is specifically disclosed as a working example within claims 5-6 of the '618 patent.

RESPONSE TO REMARKS: At p. 8 of the instant remarks, applicant states that a terminal disclaimer will be filed to overcome this rejection after the examiner determines the claimed subject matter to be allowable. This is not found persuasive and the rejection is maintained.

[8] The rejection of claims 22-24, 30-32, and 35-36 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 4, 11-12, 15, and 17 of US Patent 7,202,059 B2 (hereafter "'059 patent") in view of Dörschug (*supra*), Schmid et al. (US Patent 5,919,895; cited in the PTO-892 mailed on 12/12/08; hereafter "Schmid"), and Badziong et al. (US Patent 5,866,371; hereafter "Badziong") is maintained for the reasons of record and the reasons set forth below.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Regarding claims 31 and 35, the differences between claims 2 and 4 of the '059 patent and claims 31 and 35 herein are:

1) claim 31 of this application requires protein(Y) to be mini-proinsulin, whereas "Y" of the '059 patent is pro-insulin or insulin;

2) claim 31 of this application requires a Lys or Arg codon (moiety Z) before Hir, which is not required in claim 2 of the '059 patent; and

3) claim 31 of this application requires Px to be a yeast AHD2 promoter and Sx to be a nucleic acid encoding an alpha factor leader sequence, whereas P and S of claim 2 of the '059 patent are generic with respect to the promoter and nucleic acid encoding a signal sequence.

However, in view of the teachings of the references of Dörschug, Schmid, and Badziong, these differences would appear to be obvious variations of the claims of the '059 patent. Regarding **difference 1)**, Dörschug teaches mini-proinsulin is a form of pro-insulin with a shortened B or C chain and is easily converted to insulin (column 1, lines

8-34). Regarding **difference 2)**, Schmid teaches the advantage of placing an Arg at the N-terminus of a recombinantly expressed hirudin allows for removal of a fused signal sequence with trypsin (column 2, line 66 to column 3, line 1). Regarding **difference 3)**, Dörschug teaches a yeast expression vector encoding a yeast alpha factor precursor sequence (column 9, Example 6; column 3, lines 18-25; Figures 2a and 2b), which is considered to be a nucleic acid encoding an alpha factor leader sequence and Badziong teaches the use of a yeast ADH2 promoter (ADHII in Badziong) for recombinant expression of miniproinsulin and hirudin in yeast, which results in high yields (column , lines 16-20; column 3, lines 10-12).

Therefore, in view of the noted teachings of Dörschug, Schmid, and Badziong, it would have been obvious to modify the nucleic acid of the '059 patent to: 1) have "Y" be mini-proinsulin; 2) encode Arg at the N-terminus of Hir; and 3) for P and S to be a yeast ADH2 promoter and an alpha factor leader sequence, respectively. One would have been motivated to make such modifications and to have a reasonable expectation of success because: 1) the prior art recognizes yeast as a suitable expression host for a mini-proinsulin fusion protein; 2) Arg at the N-terminus of Hir allows cleavage of the hirudin moiety from the signal sequence as taught by Schmid; and 3) the use of yeast ADH2 promoter and an alpha factor leader sequence for high yield production of a heterologous protein is shown by the prior art.

Regarding claims 22-24, 30, and 36, in addition to differences 1) to 3) addressed above, the differences between claims 2, 11-12, and 17 of the '059 patent and claims 22-24, 30, 36, and 41 herein are:

4) claims 36 and 41 of this application require the host cell to be a yeast host cell; whereas claims 2, 11-12, and 17 of the '059 patent are generic with respect to the host cell;

5) claims 22-23 of this application require adjusting the pH of the supernatant to about 2.5 to 3.5 to precipitate non-desired proteins, whereas claim 13 of the '059 patent recites a precipitation step, yet does not expressly recite adjusting the pH to about 2.5 to 3.5;

6) claim 24 of this application requires a "releasing" step prior to concentrating the protein encoded by Y, whereas the fermentation methods of claims 11-12 of the '059 patent do not require a "releasing" step prior to concentrating the protein encoded by Y; and

7) claim 30 of this application requires "releasing" by treating the fusion protein with trypsin and carboxypeptidase B.

However, in view of the teachings of the references of Dörschug, Schmid, and Badziong, these differences would appear to be obvious variations of the claims of the '059 patent. Regarding **difference 4)**, Dörschug and Badziong teach expression of a mini-proinsulin protein using a yeast host cell and expression vector (*e.g.,* columns 9-10, Examples 6-7). Regarding **difference 5)**, Dörschug teaches precipitating undesired elements from the supernatant by adjusting the pH to 3.5 (column 8, lines 4-6; column 10, lines 61-65). Regarding **difference 6)**, claim 17 of the '059 patent expressly recites a "releasing" step prior to isolating insulin. Regarding **difference 7)**, Dörschug teaches

preparation of insulin from mini-pro-insulin using a combination of trypsin and carboxypeptidase B (column 12, lines 11-22).

Therefore, in view of the noted teachings of Dörschug, Schmid, and Badziong, it would have been obvious to modify the nucleic acid and method of the '059 patent to: 4) produce the fusion protein using a yeast host cell and expression vector; 5) adjust the pH of the supernatant to 3.5; 6) to release mini-proinsulin prior to concentrating by enzymatic or chemical cleavage; and 7) treating mini-proinsulin with trypsin and carboxypeptidase B for conversion to insulin. One would have been motivated to make such modifications and would have had a reasonable expectation of success because: 4) the prior art recognizes yeast as a suitable host for high level heterologous protein expression; 5) to remove undesired elements from the supernatant as taught by Dörschug; 6) release the elements of the fusion protein as recited in claim 17; and 7) convert mini-proinsulin to insulin as taught by Dörschug.

Regarding claim 32, in addition to differences 1) to 7) addressed above, the difference between claim 2 of the '059 patent and claim 32 herein is: 8) claim 32 requires a sequence encoding Gly-Asn-Ser-Ala-Arg between the sequences encoding hirudin and protein Y moieties. Claim 32 cannot be considered patentably distinct over claim 2 of the '059 patent when there is a specifically disclosed embodiment in the '059 patent that supports claim 2 of the patent and falls within the scope of claim 32 herein because it would have been obvious to one of ordinary skill in the art to include a sequence encoding Gly-Asn-Ser-Ala-Arg between the sequences encoding hirudin and protein Y moieties by selecting a specifically disclosed embodiment that supports that

claim. See, *e.g.*, column 7, lines 62-64, which discloses a nucleic acid encoding a hirudin-proinsulin fusion protein with a sequence encoding Gly-Asn-Ser-Ala-Arg between the sequences encoding hirudin and proinsulin. One of ordinary skill in the art would have been motivated to include a sequence encoding Gly-Asn-Ser-Ala-Arg between the sequences encoding hirudin and protein Y moieties because that embodiment is disclosed as a working example within claim 2 of the '059 patent.

RESPONSE TO REMARKS: Beginning at p. 8 of the instant remarks, applicant argues that at the time of the invention, it was not predictable that a mini-proinsulin fusion protein having hirudin at the N-terminus could be exported from yeast "in good yields" that are significantly higher than 100 mg/mL. Applicant relies on the references of Kjeldsen, T. (*Appl. Microbiol. Biotechnol.* 54:277-286, 2000) and Kjeldsen et al. (*J. Biol. Chem.* 277:18245-18248, 2002) to support a position that the prior art did not provide a reasonable expectation of achieving recombinant insulin secreted at yields significantly higher than 100 mg/L in a properly-folded, stable conformation using yeast as an expression host.

Applicant's argument is not found persuasive. Regarding applicant's argument that there was no expectation of achieving yields that are significantly higher than 100 mg/mL using yeast as an expression host, it is noted that the claimed nucleic acid (claims 31-32 and 35) and processes (claims 22-24, 30, and 36) do not recite a limitation requiring a particular yield of fusion protein to be expressed and secreted. In this case, the feature upon which applicant relies (i.e., fusion protein yield that is

significantly higher than 100 mg/L) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, there is no teaching or suggestion in the prior art of record that would teach away from making the claimed nucleic acid or practicing the claimed processes *as written*.

Regarding applicant's argument that one would have expected that mis-folding could occur and the stability of the fusion protein could not have been predicted, the claimed nucleic acid (claims 31-32 and 35) and processes (claims 22-24, 30, and 36) do not recite a limitation requiring a particular yield and level of stability of the fusion protein. Moreover, applicant has provided no evidence to support the position that one of ordinary skill in the art could have expected mis-folding to occur or would have doubted the stability of a fusion protein when using yeast as an expression host and arguments of counsel cannot take the place of evidence in the record. See MPEP 2145.I.

Beginning at p. 11 of the instant remarks, applicant argues the yield of insulin obtained by the claimed processes is "unexpected" and "superior to that described in literature" and the disclosed method provides the advantage of avoiding structural engineering to enhance yield.

Applicant's argument is not found persuasive. Regarding applicant's assertion of an unexpected yield of insulin that is significantly higher than 100 mg/L, as noted above, the claimed nucleic acid (claims 31-32 and 35) and processes (claims 22-24, 30, and

36) do not recite a limitation requiring a particular yield of fusion protein to be expressed and secreted. As such, applicant's alleged "unexpected results" are not commensurate in scope with the claimed invention. See MPEP 716.02(d).

Conclusion

[9] Status of the claims:

- Claims 22-24, 30-32, and 35-36 are pending.
- Claims 22-24, 30-32, and 35-36 are rejected.
- No claim is in condition for allowance.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656